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OFFICE OF THE CHIEF EXECUTIVE OFFICER / MEDICAL DIRECTOR

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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To Whom It May Concern:

Community Blood Center/Community Tissue Services (CBC/CTS) appreciates the opportunity to comment on the FDA Draft Guidance for Industry entitled Collection of Platelets by Automated Methods.

Founded in 1964, CBC is a quality, comprehensive provider of blood components, laboratory services, transfusion medicine, and therapeutic blood services in the Miami and Whitewater Valleys. CBC is a not-for-profit, charitable organization, servicing the blood needs of twenty-seven hospitals. The Dayton Headquarters is open to donors six days a week and additional days based upon need. The Center delivers blood to all hospitals served and handles emergencies on a seven days per week, twenty-four hours a day basis. CBC operates four branch blood collection centers for the convenience of donors in Middletown, West Chester, and Springfield, Ohio, and Richmond, Indiana. The Apheresis department operates at the Dayton Headquarters and the Springfield and West Chester branches. Mobile blood drives including apheresis collections are scheduled throughout fifteen counties to help assure that donations will be sufficient to meet patient blood needs. CBC is accredited as a Regional Marrow Donor Center, and operates Reference and Stem Cell Laboratories accredited by the American Association of Blood Banks. The principal role of CBC is service to the patients.

We thank FDA for providing updated guidelines for platelet pheresis. We can understand what a monumental task this must have been for those involved. Please consider the following comments prior to finalizing the guidelines.

This draft guidance appears to present FDA's attempt at updating and consolidating all relevant information for manufacture of platelets collected by automated methods, including guidance on licensing applications. Bringing all of this information into one document should assist the community in executing the appropriate activities for collection of platelets by automated methods. In this attempt, however, the FDA is imposing various activities and restrictions which are likely to increase the costs to the health care system and reduce platelet availability while not contributing any incremental advancement to the safety of the blood supply or to the safety of the blood donor. FDA has not provided adequate data to support such changes in practice, for example, serious injuries or death that will be avoided if the provisions were implemented. Even though these provisions are in the form of a Guidance and thus do not create legally binding requirements, the agency should be aware that by

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common practice any such statements in Guidance are taken by the blood establishments as a Rule.

Specific Comments:

III. DONOR SELECTION AND MANAGEMENT
A. Donor Selection
• Prior to the first donation, test Platelets, Pheresis donors for levels of the following laboratory values that are acceptable under the manufacturer's directions for use:
• WBC count

Comment - WBC count is required prior to first collection. There is no obvious reason for this requirement, and no parameters for donor acceptance. We do not measure the white count for many other collections. In addition, there are no manufacturer's directions for use with regard to WBC count, nor is there any other reason stated for which the WBC should be evaluated.

Recommendation – Remove the requirement for WBC counts.

You should not collect Platelets, Pheresis from donors who have ingested drugs that adversely affect platelet function. These include, but may not be limited to:
• Aspirin (ASA)/ASA-containing drugs – 5 days from last dose (Ref. 10)

Comment - One of the key articles in the literature demonstrated that:

- Platelets from donors who have ingested aspirin 36 hours before donation are hemostatically effective, because enough new platelets are released that can bypass the metabolic blockade in the aspirin-treated platelets and make the group as a whole quite functional.
- Bleeding times are improved if the recipient contributes 10 to 20% of the platelet pool even though the donor's platelets have been exposed to aspirin one hour previously.
- Only 5% of normal platelets were required to cause biphasic epinephrine-induced aggregations which will have a positive effect even on those platelets inhibited by aspirin.

In this same article, the authors also demonstrated that platelet function (as measured by bleeding times and epinephrine-induced platelet aggregation) returned to baseline value 48 to 72 hours after the ingestion of 600 mg of aspirin.

(Stuart MJ et al: Platelet Function in Recipients of Platelets from Donors Ingesting Aspirin. NEJM 1972; 286:1105-1109.

Other articles have demonstrated that, although ASA is an irreversible inhibitor of cyclooxygenase, once stopped, the platelets produced by the bone marrow (about 10% of the population per day) are unaffected. Most studies have shown that only 10-20% of unaffected platelets are needed for total platelet function to be normal.

Recommendation - We recommend retaining the current criteria of deferring donors for 36 hours from the last dose.

• Non-steroidal Anti-inflammatory Drugs (NSAIDS) – 3 days from last dose (Ref. 9)

Comment – It is generally agreed that NSAIDS are reversible inhibitors of platelet function and that the platelets will function in the recipient (as long as the recipient is not on NSAIDS). The citation for this change is the website for the military deferral rules. In addition to the fact that this is not a legitimate scientific reference, it is misquoted. The military defers these donors for one day, not five.

Recommendation - There should be no deferral for ingestion of NSAIDS.

B. Donor Management

1. Platelet Count

• You should perform a pre-donation platelet count (Ref. 10), which will allow the device operator to more accurately set the target platelet yield parameters for each collection of Platelets, Pheresis. This is consistent with the device manufacturer's directions for use.

• For any collection facility that cannot perform a pre-donation platelet count (for example, a mobile collection site), you should use a platelet count as specified by the device manufacturer, or a post-donation count from a previous collection to set the target platelet yield. You should collect only a single Platelets, Pheresis collection from first-time donors who do not have a pre-donation platelet count.

• You should defer from donation donors whose platelet counts are less than 150,000/uL until a subsequent platelet count indicates that the donor's platelet count is at least 150,000/uL.

Comment - This requirement appears to be intended to serve as a donor safety function, as well as ensuring an adequate collection. To ensure donor safety, since a single collection reduces the platelet count by about one third, the requirement for

150,000 is appropriate. However, many apheresis donors are regular, frequent donors. In locations where a pre-count is not available at the time of collection, we, and many other centers, use the average of the three prior pre-counts to set the machine. Since platelet counts are performed on every collection, the therapeutic dose is confirmed by these counts, not by the donor count.

> ***Recommendation*** - We believe that the requirement for post counts should be eliminated in all areas of the Guidance.

2. Donation Frequency
To protect the safety of the donor:
• A donor should undergo no more than 24 Platelet, Pheresis collections in a 12-month period.
• You should collect no more than 24 total Platelets, Pheresis components in a 12-month period. Two components collected from a double collection of Platelets, Pheresis and three components collected from a triple collection of Platelets, Pheresis would be counted as two components and three components respectively.
• The interval between each collection of Platelets, Pheresis should be at least two (2) days with no more than two procedures in a 7-day period.
• The interval between collection of a double Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 7 days.
• The interval between collection of a triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 14 days.
• A post-donation platelet count should be performed after each collection.

Comment -Limiting Platelet, Pheresis components to 24 a year is upsetting to those donors who take great pride in helping their community. They do not understand, after all these years and no apparent ill effects, why such a rule would be instituted. As healthy individuals and after many donations, they have great concerns about how this limitation will affect the area's blood supply; some are very disgruntled. Studies (such as Glowitz and Slichter. Frequent Multiunit Plateletpheresis from Single Donors: Effects on Donors' Blood and Platelet Yield Transfusion 1980:20(2); 199-205) have demonstrated both the safety to donors (with rebound of donor platelet count), and adequacy of collections, in frequent apheresis donors.

Besides reducing the availability of needed components, operationally, changing the criteria to monitor components collected instead of donations, could be a logistic nightmare, as the computer tracking systems were designed to track donor eligibility

based on donation interval, not products collected. This type of computer change cannot be done by the blood center, but requires vendor software modification significant enough to affect 510(k) clearance of the device. These computer changes are costly, time-consuming and during their development, the manual workaround would be fraught with error.

> ***Recommendation*** – Retain current guidelines for frequency of platelet apheresis procedures in a donor.

4. Total volume loss per collection procedure
The total volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should not exceed 500 mL (600 mL for donors weighing 175 lbs or greater) or the volume described in the labeling for the device, whichever is less.

Comment - All apheresis equipment is programmed based on donor height, weight and hematocrit to ensure adequate plasma collection to support platelet viability through storage and prevent excess plasma loss based on donor size. The acceptable volume of donation should be defined in the licensure of the collection device and not determined at the time of collection.

> ***Recommendation*** – Total plasma loss should be according to machine criteria and donor weight.

D. Medical Coverage
Under 21 CFR 640.22(c), the procedure for collection of Platelets, Pheresis, including the availability of medical care during the donation, must conform to the standards described in the biologics license application or supplement.

We believe that a physician should be present on the premises during the collection of Platelets, Pheresis to ensure that necessary medical treatment be available to the donor in a timely fashion.

We interpret "present on the premises" to include a qualified physician able to arrive at the premises within 15 minutes (Ref. 11). In case of an emergency, calling 911 may be used to obtain emergency medical care and transportation to another facility for further care, but we do not believe this is a sufficient substitute for an available physician as previously described.

Comment – The intent of this section is to provide the appropriate and timely donor care in case of a reaction. There is no evidence that a physician qualified in Transfusion Medicine (or other specialties likely to be on a Blood Bank staff) is more able to deal with an emergency than Emergency Medical Technicians. Besides being better trained in emergency management, the response time for 911 is often shorter than the 15 minutes required by the proposed guidance. In addition, because the extracorporeal red cell volume with current apheresis equipment is significantly less than that removed by a whole blood donation, reaction rates are, in fact, significantly lower in apheresis donor than in whole blood donors. Operationally, about 25% of our Platelet, Pheresis collections occur on mobiles, and the ones at our fixed sites may occur at hours when the staff physicians are not present or out of center. The requirement for a physician would significantly reduce the availability of needed components for the patients in our hospitals. Apheresis donation of blood products has a long history of being a safe and efficient mechanism of collecting the required blood products for the nation and no significant change has been identified to suggest that this activity has resulted in a risk that warrants this level of physician involvement.

> ***Recommendation*** – Remove this requirement and allow centers to develop their own emergency response plans.

IV. INFORMATION PROVIDED TO THE DONOR

Under 21 CFR 640.22(c), the collection procedure, including the information provided to the donor, must conform to the standards described in the biologics license application or supplement. Platelets, Pheresis donors should receive information about the collection procedure and its associated risks. You should provide Platelets, Pheresis donors with the same information that you provide a Whole Blood donor, plus the following information specific to the platelet collection:
• A description of the number of Whole Blood, apheresis Red Blood Cells or plateletpheresis collection procedures and/or components that may be collected per year, and the donation interval for each.

Comment -- This requirement will lead to an inordinately complex and lengthy description for donors. At the time the information is provided, most donors will not know which product (single/double/triple) they will give, since this will be based on their individual counts. This requirement constitutes elements for collectors rather than elements of consent. In addition, it would be nearly impossible to develop a document that contains all the scenarios that donors would actually take the time to read. The relevance of this to the donor education process is not obvious.

Recommendation – Change the requirement to state that the information provided should include only the number of procedures that may be performed per year.

V. COMPONENT COLLECTION AND MANAGEMENT

B. Target Platelet Yield

To assure that each component obtained from a multiple collection of Platelets, Pheresis results in an actual platelet yield of at least 3.0×10^{11} platelets, you should use the following targets. When collecting:

- Double components, the device's target platelet yield setting be at least 6.5×10^{11}.
- Triple components, the device's target platelet yield setting be at least 10.0×10^{11}.

Comment - Apheresis collection facilities experience different precision with respect to platelet yield predictions based on laboratory methods, hematology analyzers, apheresis practices, and apheresis device. The manufacturers of the apheresis devices are practiced and expert in guiding the facility in understanding this precision and how to determine appropriate yield targets. It is inappropriate for the agency to set these targets since there is such a widely variable range of experience for each technology. These defined numbers are currently incorrect for many locations and will not stand the test of time for new product developments as technology improves. This standard can be expected to reduce the efficiency of collection and provision of platelet products from current levels. It is most beneficial for the agency to set the minimum limits (i.e., 3.0×10^{11} per therapeutic dose).

Recommendation - We recommend that FDA remove this requirement, and instead encourage facilities to utilize validation and monitoring data and work with the respective manufacturer to determine the appropriate target yields.

VI. PROCESS VALIDATION

In addition, you should perform Process Validation on the following devices used in the collection process:

- Blood cell counting devices, including devices used to determine the residual WBC count in leukocyte reduced components.
- pH measurement:

We recommend that a pH meter be routinely used rather than pH (nitrazine) paper.

- The scale used to weigh the components

• Sterile tubing welders used to attach leukoreduction filters or sampling containers (Ref. 13)
• Shipping containers

Comment - The devices listed are not used in the collection process, with the possible exception of tubing welders. Rather, these are devices that may be used in the preparation, shipping and measurement of platelets, pheresis. We believe validation of a Class I device, per se, is not needed. Appropriate training and demonstration of proficiency of the technologist would apply. Even properly installed, calibrated and functioning devices, as the agency notes later in the document, will not assure the proper use. We believe the goal is better served with a focus not on the devices but on the entire process.

Recommendation – Alternate wording - "In addition, you should perform Process Validation on the following processes used in the preparation, shipping and measurement of platelets, pheresis:

- Blood cell counting: platelets, WBC and residual WBC
- pH measurement: We recommend that a pH meter or blood gas analyzer be routinely used rather than pH (nitrazine) paper.
- Component weighing
- Sterile connection methods
- Preparation of blood components for shipping: Shipping containers should be appropriate for this purpose."

B. Validation Protocol
The validation protocol should include at least the following:
• A description of the equipment to be used
• Minimum/maximum acceptable values for the Platelets, Pheresis collection and/or component as specified by the device manufacturer (see 21 CFR 606.60(a)).
- Total volume (after removal of samples for testing and bacterial contamination testing), including per component (container) from double and triple collections
- Target platelet yield

Comment - Specifying a minimum/maximum value for a "Target platelet yield", which is a fixed value, does not make sense in this context.

Recommendation - We suggest this be removed.

D. Product Performance Qualification (Component Collection)
Qualification should include testing for the actual platelet yield, pH, volume, residual WBC count and percent component recovery (for leukocyte reduced components), RBC/hematocrit (if applicable) and bacterial contamination testing (Table 1).

Comment - Percent component recovery applies only to leukocyte reduction by filtration and not by process. RBC/hematocrit is not associated with any specification; therefore it should be dropped from the performance qualification. Also, the guidance uses terminology of "per container" which we believe means per therapeutic dose. However, the agency should be cognizant of the fact that in many systems a single therapeutic dose can and at times must be held in more than one container to preserve the proper storage conditions.

> ***Recommendation*** - Suggest rewording as follows: "Qualification should include testing for the actual platelet yield, pH, volume, residual WBC count and percent component recovery (if applicable), and bacterial contamination testing."

"You should use the following collection performance qualification criteria:

- Test a minimum of 60 consecutive single (30 for double and 20 for triple) collections for each type of automated blood cell separator for (1) actual platelet yield, pH, volume, visible RBCs; and (2) for residual WBC count and percent recovery (Ref. 2), with 0 failures in each category. Another option is to test 93 consecutive single (47 for double and 31 for triple), which allows for 1 failure. Perform bacterial contamination testing on 500 collections with 0 failures. Refer to Table 1. Determine the sample size selection before starting the qualification process. For example, if you test 60 and encounter a failure, you should not continue with the testing of an additional 33 components."

Comment 1 - Visible RBCs - There are no specifications for "visible RBCs" in the platelets. Contamination with 2mL of RBC in platelets, pheresis is grossly obvious, due to unusual special causes, and can be incorporated into routine SOPs and need not be required in the process validation phase.

> ***Recommendation*** - Remove the requirement from the qualification testing criteria.

Comment 2 - Yield- As is well known in the industry and to the agency, automated instruments currently available that are used for counting platelets in whole blood samples of patients provide widely divergent platelet counts when applied to platelet-rich plasma from platelet components and platelets, pheresis. Therefore, the state-of-the-art interlaboratory accuracy of this outcome over the entire country does not support an overly restrictive requirement for platelet yield. The current FDA thinking (Ref. 1) states 75% of products should be $>3.0x10^{11}$. Industry standards call for at least 90% should be $\geq 3.0 \times 10^{11}$. We believe there is no medical argument for a stricter interpretation resulting in a change in the historical definition for a therapeutic dose.

> ***Recommendation*** - We propose the target criteria for a therapeutic dose be 90% $\geq 3.0x10^{11}$ with 90% confidence. These criteria would also apply to divided collections (e.g., doubles and triples).

Comment 3 - Volume - It is not clear what the agency intends with the volume criteria: "Double collections: each container contains 50% +/- 5%. Triple collections: each container contains 33% +/- 3%." Perhaps the agency means that the net volume of each therapeutic dose should be 50% of the original collection volume for a double collection and 33% of the original collection volume for a triple collection.

> ***Recommendation*** - We propose there should be no volume specification for divided products beyond the manufacturer's criteria for storage containers and minimum therapeutic dose for platelets of $3x10^{11}$ platelets. We further recommend the target criteria be 90% compliance with 90% confidence, reflecting the current industry approach to platelet yield.

Comment 4 – Bacterial Contamination – FDA has not required any bacterial testing for release of platelets, but has accepted AABB standards as quality control. Therefore, any requirements in the guidance should be consistent with quality control, and not overly restrictive.

> ***Recommendation*** - We believe bacterial testing for qualification purposes may be conducted concurrently with implementation of the preparation method. Bacterial testing should be conducted according to industry standard using a method cleared for QC by FDA for the first 2 months of use. The expected outcomes of bacterial testing with anaerobic culturing methods on a broad scale is not known at this time. Therefore, we suggest more general wording for the target criteria and indications for follow-up.

- "For facilities using automated blood cell separators from a single manufacturer only, we recommend that:
    - All devices be included in the initial product performance qualification; and
    - Additional devices of the same model be included in monthly QC testing only.
- Product performance qualification should be completed for each automated blood cell separator used in your establishment."

Comment - Automated collection processes are defined by the device make and model (e.g., Baxter Amicus, Gambro Trima Accel, Haemonetics MCS+). Therefore, initial performance qualification should be performed by device type. In the context of process validation, we believe if all fixed and mobile sites of a licensed establishment operate under the same standard operating procedures, training program, etc. performance validation should be performed by the institution for each type of device make and model.

> ***Recommendation*** – Suggested wording - "Product performance qualification should be completed for each automated blood cell separator (defined as type and model) used in your establishment. All devices should be included in the initial product performance qualification; and devices added following the initial qualification of the same type and model should be included in monthly QC testing only."

"Testing be conducted on both containers from double collection and on all three containers for triple collection;"

Comment - Testing on each container of multiple product collections is performed during validation testing. Once the process is validated, it should be clear that this level of testing is only required as part of monthly QC.

> ***Recommendation*** – Remove this statement.

"Residual WBC count be performed within 24 hours of collection, or per the manufacturer's direction for the cell counting methodology (Ref. 2);"

Comment - No manufacturer currently requires processing within 24 hours. As stated, 24 hours will be interpreted as the maximum time, and will impose an undue burden on some blood establishments.

Recommendation - Maintain the following wording "Samples should be handled, prepared and processed without delay according to the requirements of the counting method to ensure that a true and representative count is obtained."

- "An RBC count/hematocrit be performed on Platelets, Pheresis or concurrent Plasma (when collected) containing visibly apparent RBCs to determine total packed RBC volume. You should hold Platelets, Pheresis containing more than 2 mL of RBCs until the residual WBC count has been determined and found to be less than 5.0×10^6 for platelet or plasma components labeled as leukocyte reduced;"

Comment - There are no specifications associated with residual RBC in platelet products, therefore, this should be dropped from the qualification criteria. The specific action stated for platelets (we assume the agency means by therapeutic dose) should be included in an operational SOP, but not the qualification plan.

Recommendation – Remove this statement.

- "Test one third of the components collected for qualification during the first third of the dating period; one third during the second third of the dating period, and one third the day of outdate. For example, for Platelets, Pheresis with a 5-day dating period, test one third at 1-2 days, one third at 3-4 days and the final third on day 5 after collection. Components that expire may be used for qualification if tested within 12 hours after expiration. You should not release such outdated components for transfusion, however."

Comment - The only criteria that are expected to change over the course of storage are pH and titer of contaminating bacteria. Although not stated, we presume the agency intends this to be directed at pH only. We disagree that testing platelets over the storage period will contribute any meaningful information to the qualification scheme. The manufacturers have already presented data as a basis of approval which shows storage characteristics if the device is used according to the manufacturer's directions for use. This exercise

does not demonstrate that the device performs according to the manufacturer's claims in the local facilities hands.

- "Conduct an investigation of component qualification failure, and when appropriate, initiate corrective action and follow-up measures. We understand that some failures may occur due to conditions **not** resulting from a failure of the process. Examples of non-process failures include positive bacterial contamination testing resulting from the collection from a donor with asymptomatic bacteremia."

Comment - Interpretation of a positive bacterial test which may be from a transiently bacteremic donor may prove to be difficult.

Recommendation - Reword as follows - "Positive bacterial contamination testing which may have resulted from the collection from a donor with asymptomatic bacteremia, even though the bacteremia cannot be confirmed."

VII. QUALITY ASSURANCE (QA) AND MONITORING

A. Standard Operating Procedures (SOPs) and Record Keeping

1. Requirements for SOPs

• You must ensure that the automated blood cell separator "perform[s] in the manner for which it was designed" (21 CFR 606.60(a)) during the collection or processing of apheresis components. Written SOPs must be maintained and must include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components (21 CFR 606.100(b)). Therefore, you must have written SOPs for each function in the collection of Platelets, Pheresis, including all of the sections described in this guidance.

• Your written SOPs must include minimum and maximum values for a test or procedure when it is a factor in determining donor acceptability (21 CFR 606.100(b)(2)).

• Your written SOPs must include procedures for investigating adverse donor and recipient reactions (21 CFR 606.100(b)(9)).

2. Additional Provisions Applicable to SOPs

• Actual platelet yield: The platelet yield from each collection of Platelets, Pheresis should be provided to the transfusion facility.

Comment - We assume the intent is per therapeutic dose, rather than each collection. There is a minimum therapeutic dose requirement for each issued platelet product.

The precise value is not used by the clinical service in prescribing treatment for the patient, and providing it for all products will not improve the care given the patient. The platelet content is available upon request of the clinical facility.

> ***Recommendation*** – Reword as follows: "The platelet yield from each therapeutic dose of Platelets Pheresis should be provided to the transfusion facility when the yield is $< 3.0x10^{11}$."

• **Residual WBC counts**: Your SOP should state the maximum acceptable WBC limits for each automated blood cell separator device in use.

Comment - The maximum acceptable residual WBC limit for apheresis platelets established by AABB Standards is $5x10^6$ per unit or therapeutic dose.

> ***Recommendation*** – Reword as follows: "Your SOP should state the expected WBC limits as defined by the manufacturer's instructions, as well as the maximum acceptable WBC limits of $5x10^6$ per unit or therapeutic dose as defined by AABB Standards."

• **Total volume loss**: Annual volume loss should not exceed 12 liters (12,000 mL) per year for donors weighing 110 – 175 lbs; 14.4 liters (14,400 mL) per year for donors weighing more than 175 lbs) (Ref. 3).

Comment – Use alternative language for Total Volume Loss.

> ***Recommendation*** - Total Plasma Volume Loss should replace Total Volume Loss.

• **Labeling**:
o For Platelets, the volume range reported on the label must be within reasonable limits (21 CFR 606.121(c)(6)). You should determine the final component volume to be stated on the label after removal of samples for platelet count determination, QC and/or bacterial contamination testing.
o Platelets, Pheresis routinely should contain no less than 3.0×10^{11} platelets per storage container. When special circumstances warrant their use, Platelets, Pheresis components containing less than 3.0×10^{11} platelets per storage container should be labeled with the actual platelet content.

Comment - Single therapeutic doses of platelets may be, and at times must be stored in 2 containers based on the specifics of the storage container and manufacturer's recommendations.

> ***Recommendation*** - Alternative language for Labeling: "Platelets issued as a single therapeutic dose that contain less than $3x10^{11}$ platelets should be labeled with the actual platelet content."

B. Donor Monitoring

1. Platelet counts

You should notify your Medical Director when a donor has a post collection platelet count less than 100,000/uL, and you should defer the donor until his/her platelet count has returned to at least 150,000/uL. Transient decreases in platelet counts have been reported in donors undergoing multiple collections of Platelets, Pheresis (Ref. 21). Although the effect of long term regular collection of Platelets, Pheresis on donor platelet counts is unknown, clinically significant thrombocytopenia in these donors is unusual. You should review a donor's records before each donation to monitor the donor's ability to recover his/her baseline platelet count.

Comment - We disagree that post donation platelet counts should be performed after donation.

> ***Recommendation*** - Alternative language for Platelet Count: "Determination of donor post donation platelet counts is not required. However, if a post donation platelet count is known to be less than 100,000/uL, you should notify your Medical Director. You should defer the donor until his/her platelet count has returned to at least 150,000/uL."

C. Component Testing

1. Daily component specification check

• Actual platelet yield after collection: Actual yields (volume x platelet count) must be determined at the conclusion of each appropriate phase of manufacturing (21 CFR 211.103), and should be determined prior to issue.

Comment - 21 CFR 211.103 specifically refers to finished pharmaceuticals. Platelets, Pheresis are a biologic product. We believe this requirement is misplaced and, if applied to platelets, could result in needless loss of platelets for sampling. There are multiple phases of processing that platelets undergo from collection to issue, and we

feel the definition of "each appropriate phase of manufacturing" is ambiguous. We do agree that the yield of the product should be determined prior to issue.

> ***Recommendation*** - Alternative language for Actual platelet yield after collection: "Actual yields (volume x platelet count) should be determined prior to issue."

o Weight/volume conversion: A weight/volume conversion is necessary to determine the volume.

Comment - Consistency of practice would be enhanced by the document stating what specific gravity should be used.

> ***Recommendation*** - A specific gravity of 1.05 g/mL is suggested.

• Residual WBC count on all collections that do not utilize an automated leukocyte reduction methodology.

Comment -- Universal leukoreduction is not required.

> ***Recommendation*** - We suggest that FDA remove this requirement.

• Bacterial contamination testing: as specified by the collection device manufacturer.

Comment - Collection device manufacturers do not require bacterial contamination testing (e.g., method and frequency). Bacterial testing is required by industry standard (AABB), and in some instances (e.g., 7-day platelet storage) specified by the device manufacture.

> ***Recommendation*** - Alternative language for bacterial contamination testing: "Bacterial contamination testing should be conducted at the frequency and by the method established by the blood center after consideration of industry standards and any specific requirements by device manufactures."

2. QC monitoring
Under 21 CFR 211.160(b), laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures One example of a scientifically sound statistical sampling plan is the use

of scan statistics (see Appendix A). However, other statistical plans may also be appropriate.

Comment - The common practice of taking Guideline statements as a Rule will also be applied to the agency's suggested use of scan statistics. We recognize and appreciate that CBER has devoted time and effort to this approach resulting in an intellectual contribution to the field (ref. Journal of Biopharmaceutical Statistics 2005:15;353-366.). However, we feel strongly that it is premature to add this to the Guidance document. We feel the agency should first partner with a variety of blood establishments (e.g., large, small, centralized, distributed) and conduct pilot studies to ascertain the true burden this may place on facilities. It may be true that the scan statistics approach will fit very well in some situations, but on the other hand, it may be that the inspection burden would be overwhelming in other situations. By placing this so prominently in the Guideline, FDA is, by default, requiring this to be implemented. We believe the burden of proof resides with the agency to demonstrate the utility of this approach in real life situations prior to including in a Guidance, much as we would expect clinical evidence to be presented prior to implementing a change in clinical practice.

X. REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)

Comment - We believe that the requirement to send platelet products to CBER for testing is an outdated practice that does not make a meaningful contribution to the safety and efficacy of the product or manufacturing process. Since this practice was initiated, the technology for collection and laboratory methods have made tremendous strides and progressed through several generations of development. We suggest that FDA can obtain all necessary information related to the manufacturing process of platelets, pheresis through examination of the qualification and QC records from the facility. At this point, we believe this activity unnecessarily consumes people resources at the blood centers and CBER as well as valuable blood products that could go to patients. This requirement is not applied to red blood cell products or plasma products.

***Recommendation*:** Remove this statement.

Again, Community Blood Center/Community Tissue Services appreciates the opportunity to comment on this draft guideline. We request that FDA take our comments into consideration prior to finalizing the document.

Sincerely,

Judith E. Woll, M.D.
CEO

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Director, Quality Assurance